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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/787,526 | 02/26/2004 | C. Allen Chang | 3102/2020 | 6448 |

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| EXAMINER | |
|---|---|
| JONES, DAMERON LEVEST | |
| **ART UNIT** | **PAPER NUMBER** |
| 1618 | |

DATE MAILED: 05/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/787,526 | CHANG ET AL. | |
| | Examiner | Art Unit | |
| | D. L. Jones | 1618 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *03 March 2006 and 26 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) *5,6,13,14 and 21-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7-11 and 16-19* is/are rejected.

7)☒ Claim(s) *12,15 and 20* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

**ACKNOWLEDGMENTS**

1. The Examiner acknowledges receipt of the preliminary amendment filed 2/26/04 wherein the specification was amended.

***Note***: Claims 1-46 are pending.

**APPLICANT'S INVENTION**

2. Applicant's invention is directed to a dual functioning excipent useful for metal chelate contrast agents as set forth in independent claims 1 and 9.

**RESPONSE TO APPLICANT'S ELECTION**

3. Applicant's election with traverse of Group I (claims 1-4, 6-12, and 14-26), drawn to excipients of the formula in independent claim 1 wherein L' is that which is disclosed in claim 4, filed 3/3/06 is acknowledged. The traversal is on the ground(s) that the restriction would result in duplicate and redundant searches for each of the groups which would be a loss of USPTO resources. This is found non-persuasive because the groups of inventions are distinct. In particular, the ligands used in the groups are structurally different and would require a separate search of the prior art. Thus, such a search is burdensome since one group of ligands would neither anticipate nor render obvious the other groups of ligands. In support of the Examiner's position, Applicant's attention is directed to the elected species and the expanded species (see below) wherein prior art renders the expanded species obvious, but neither anticipates nor

renders obvious the elected species. Hence, the restriction requirement is still deemed proper and is therefore made FINAL.

***Note***: Initially, Applicant's elected species was searched (for the elected species, in independent claim 1, the excipient is calcium bis [1,4,7-tris (carboxymethyl)-10(2'-hydroxypropyl)-1,4,7,10-tetraazacyclododecanatocalcium(II)] and elected species for independent claim 9, the excipient is calcium bis [1,4,7-tris (carboxymethyl)-10(2'-hydroxypropyl)-1,4,7,10-tetraazacyclododecanatocalcium(II)] and the metal chelate is gadolinium (III) 1,4,7-tris(carboxymethyl)-10-(2'-hydroxylpropyl)-1,4,7,10-tetraazacyclododecane.) However, since prior art could not be found to reject Applicant's claims, the search was extended to the excipient formula as set forth in independent claim 1 wherein X and X' are calcium, L' is DTPA, and both m and n are 1. For independent claim 9, the excipient is defined when X and X' are calcium, L' is DTPA, and both m and n are 1 and the metal is gadolinium(III) and organic ligand is DTPA. The search was not further extended because prior art was found which could be used to reject Applicant's claims.

It should be noted that *for the elected species*, m = 1, n=2; X = calcium; R2 = methyl; X' = calcium; Y = NR1; and R1 = hydroxylpropyl.

**WITHDRAWN CLAIMS**

4. Claims 5, 6, 13, 14, and 21-46 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention/species.

**112 REJECTIONS**

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-4, 7, and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims as written are ambiguous because it appears as if Applicant is incorporating some of the limitations of the metal chelate M(L) into the description of the variables of the excipient. However, Applicant is reminded that a recitation of intended use carries patentable weight in a method, not product, claim. Thus, claim 1 is interpreted as a product having the formula Xm[X'(L')]n. It should be noted that all claims depending upon independent claim 1, that are not withdrawn, are also ambiguous.

**103 REJECTIONS**

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-3, 7-11, and 16-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vanderipe (WO 89/00052) in view of .Rahman (US Patent No. 4,016,290)

**Vanderipe** discloses a method of enhancing the safety of metal ligand chelates as magnetic resonance and x-ray contrast agents. Paramagnetic chelates such as gadolinium diethylenetriaminepentaacetic acid (DTPA) are more toxic acutely when injected in high concentration or at rapid rates. However, the used of effective amounts of some calcium solutions substantially reduces this toxicity without the need to add additional ligand (see entire document, especially, abstract; page 1, lines 5-16; page 2, lines 22-27). The calcium may be added in a single form (e.g., calcium chloride) or as a mixture (e.g., calcium chloride and calcium gluconate) [page 3, lines 1-5]. On page 4, lines 18-31 (especially, 29-30), a ligand complex comprising GdDTPA with and without calcium is disclosed (see also page 7). Vanderipe fails to disclose a multiple calcium atoms conjugated to DTPA (excipient product) and a combination comprising multiple calcium atoms conjugated to DTPA in combination with a gadolinium-DTPA metal chelate.

**Rahman** discloses a method of transferring a polyaminopolycarboxylic acid chelating agent across a cellular membrane (see entire document, especially, abstract). In particular, it sis disclosed that polyaminopolycarboxylic acid chelating agents such as EDTA and DTPA may be encapsulated into liposomes and transferred across a cellular membrane (column 3, lines 45-47). The liposome was prepared and a calcium DTPA solution was mixed with the liposome (column 3, lines 58, through column 4, line 46).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the invention of Vanderipe using the teachings of Rahman and generate a excipient product as set forth in independent claim 1 wherein X and X' are calcium, L' is DTPA, and both m and n are 1; and an excipient product in combination with a metal chelate as set forth in independent claim 9 wherein the excipient product is defined when X and X' are calcium, L' is DTPA, and both m and n are 1 and the metal is gadolinium(III) and organic ligand is DTPA for the following reasons. Vanderipe discloses the used of calcium for enhancing the safety of metal-ligand chelates as magnetic resonance imaging or x-ray contrast agents in combination with a chelate such as DTPA. Vanderipe discloses that the calcium may be in a single form (e.g., calcium chloride) or as a mixture (e.g., calcium chloride and calcium gluconate). Thus, a skilled practitioner in the art would recognize that one may have more than one calcium atoms present. Vanderipe discloses that one may have a metal such as gadolinium present to give the species diagnostic abilities. Rahman is cited for its teachings on substances that aid in the transferring of a polyaminopolycarboxylic acid chelating agent across a cellular membrane. In particular, the reference discloses that polyaminopolycarboxylic acid chelating agents such as EDTA and DTPA may be conjugated to calcium for diagnostic/therapeutic purposes. Since both Vanderipe and Rahman disclose that calcium may be used in combination with a chelator/ligand, the references may be considered to be within the same field of endeavor; thus, the reference teachings are combinable.

**CLAIM OBJECTIONS**

9. Claims 12, 15, and 20 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

***Note***: The claims are allowable over the prior art of record for Applicant's elected species only. In particular, independent claim 1 is allowable over the prior art when the excipient is calcium bis [1,4,7-tris (carboxymethyl)-10(2'-hydroxypropyl)-1,4,7,10-tetraazacyclododecanatocalcium(II)] and the combination calcium bis [1,4,7-tris (carboxymethyl)-10(2'-hydroxypropyl)-1,4,7,10-tetraazacyclododecanatocalcium(II)] and the metal chelate is gadolinium (III) 1,4,7-tris(carboxymethyl)-10-(2'-hydroxylpropyl)-1,4,7,10-tetraazacyclododecane.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. L. Jones whose telephone number is (571) 272-0617. The examiner can normally be reached on Mon.-Fri., 6:45 a.m. - 3:15 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

D. L. Jones
Primary Examiner
Art Unit 1618

May 12, 2006